REMARKS

Claims 1-12 presently appear in this case. No claims have been allowed. The official action of August 29, 2001, has now been carefully considered. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to isolated glycosylated human tumor necrosis factor having cytotoxic biological activity, as well as methods for the preparation of such a product by recombinant techniques, compositions and methods of use.

The examiner states that the declaration is defective because it is not signed by the third inventor. This requirement is respectfully traversed.

In applicants' late submission of declaration on March 7, 2000, the first paragraph reads:

> Attached hereto are two executed oaths or declarations one signed by one inventor and the other signed by two in compliance with 37 C.F.R. 1.63, ... (4) pages

Thus, declarations signed by all three inventors were filed. Nevertheless, in case the Patent and Trademark Office lost the two pages signed by the third inventor, attached hereto is a declaration with an original signature (a photocopy having been previously filed) signed by the third inventor, thus obviating this requirement.

The examiner states that the drawings have been objected to by the draftsperson and that appropriate correction is required. Applicants will take care of making the appropriate corrections once allowable subject matter is indicated in the case.

Claims 1-6 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that claims 1, 2 and 6 are vague and indefinite in the recitation of the term "biologically active" as it is unclear what biological activity is encompassed in the claims. Therefore, the metes and bounds of the claims are unclear.

The claims have now been amended to specify that the biological activity or physiological activity referred to therein is "cytotoxic biological activity". This is supported, for example, at page 34, lines 12-13, and lines 15-19 of the present specification. Accordingly, it is believed that this amendment obviates this part of the rejection. Reconsideration and withdrawal thereof are respectfully urged.

The examiner states that claim 2 is rejected as being vague and indefinite for reciting the term "variant" because the term "variant" is not defined in the specification, and it is unclear what "variants" are encompassed in this claim.

Claim 2 has now been amended to change the term "variant" to read "mutant", which is defined at pages 33-35 of the present specification. Furthermore, the claim has been amended to specify that, in order to be a mutant, it must not only exhibit cytotoxic biological activity, but also be capable of having the cytotoxic biological activity neutralized by antisera raised against human glycosylated TNF, as is defined at page 33, lines 19-24, of the present specification. It should be understood that applicants do not contend to have made any new contributions to TNF mutants, but only to the discovery that such mutants may be made glycosylated such that they are novel and patentable for the same reason that the isolated glycosylated human TNF is patentable as described herein. Reconsideration and withdrawal of this part of the rejection are, therefore, respectfully urged.

The examiner has rejected claim 2 as being vague and indefinite in the recitation of the term "physiologically active" as it is unclear what physiological activity is encompassed in the instant claim.

Claim 2 has now been amended to specify that the physiological activity is cytotoxic biological activity, thus obviating this part of the rejection for the same reason as

discussed hereinabove with respect to the examiner's objection to the term "biologically active".

Claims 5 and 6 have been rejected as being vague and indefinite in the recitation of the term "effective amount" as it is unclear what effective amount is encompassed in the instant claims.

Claim 5 has now been amended to delete the term "effective amount" and to change the term "pharmaceutical composition" to read "composition". Accordingly, it is believed that this objection has been obviated with respect to claim 5. With respect to claim 6, this is a Jepson type claim, and the known method step is set forth in the preamble. Thus, amounts that are known to be effective are part of the prior art, and those of ordinary skill in the art already understand what amounts are effective. Furthermore, cases such as *In re Watson*, 186 USPQ 11, 20 (CCPA, 1975) confirm that the term "an effective amount" is definite in the context of a method claim which sets forth the desired result. Thus, it is definite in this case also where it is only used in the preamble of a Jepson type claim, and the processes in which the compound is used are all well known to the art. Reconsideration and withdrawal of this part of the rejection are, therefore, also respectfully urged.

Claim 2 has been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors had possession of the claimed invention. The examiner states that this is a written description requirement. The examiner states that the specification does not disclose any physiologically active variants and that the claims as written encompass nucleotide sequences which were not originally contemplated and fail to meet the written description requirement of 35 U.S.C. §112, first paragraph. This part of the rejection is respectfully traversed.

Claim 2 has now been amended to change the term "variant" to "mutant" and to define those mutants by immunological as well as biological activity. Accordingly, the genus is not "highly variant", and those of ordinary skill in the art reading the present specification understand that applicants were in possession of such mutants. This is particularly the case in view of the fact that TNF and various TNF mutants are well known in the art and are not novel *per se* in the present invention. The present invention relates to the isolation of a glycosylated form thereof. The prior art is well aware of many mutants of TNF having the properties defined in the present specification. Accordingly, those of

ordinary skill in the art would understand that applicants had possession of the present invention as claimed in claim 2 to the full scope of that claim. Reconsideration and withdrawal of this rejection are respectfully urged.

Claim 2 has also been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The examiner states that it would involve undue experimentation to determine the breadth of the term "variants". This rejection is respectfully traversed.

As indicated hereinabove, claim 2 has now been amended to define the mutants by immunological as well as biological activity, as is supported by pages 33-35 of the present specification. As the art in TNF mutants is already quite advanced and applicants have not claimed to have made any advances in the sequence of such mutants but only to the production thereof in glycosylated form, it would not take undue experimentation for one of ordinary skill in the art to practice the full scope of claim 2. Reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 1, 2 and 4 have bene rejected under 35 U.S.C. §102(b) as being anticipated by Korn. The examiner states that Korn teaches the method for producing biologically active human TNF in CHO cells and that there is no difference between the method disclosed in Korn and the one described in the

present application. This rejection is respectfully traversed.

The examiner's attention is invited to page 3, lines 16-28, of the present specification, where it states:

> Korn et al, Lymphokine Res., 7:349-358 (1988), reports the production of TNF in eukaryotic Chinese hamster ovary (CHO) cells and states that the advantage of a eukaryotic expression vector is a reduction of problems with endotoxin contamination as endotoxin may precipitate septic shock. The specific means of isolating the TNF actually used in this publication involved immunoprecipitation of the culture supernatant with polyclonal rabbit anti-TNF antibody with the immunoprecipitated material being released from SEPHAROSE beads by boiling in sample buffer containing SDS and beta-mercaptoethanol and run on a 15% SDS-polyacrylamide gel for two hours at 30 mA. Such a treatment would cause substantial loss of the biological activity of the protein. Thus, the actual product of the Korn publication is denatured and is not an isolated biologically active glygosylated [sic] TNF. Furthermore, Korn et al never recognized that the TNF produced by that method was glycosylated.

It is, thus, apparent from a study of the procedure of Korn that the actual product of the Korn publication is denatured. All of the present claims require a TNF which exhibits cytotoxic biological activity. The denatured product of Korn cannot exhibit cytotoxic biological activity. Accordingly, none of the present claims can be anticipated by Korn. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 3, 5 and 6 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Korn in view of Allet. The examiner states that Korn teaches the method for producing biologically active human TNF-α protein in CHO cells, although they do not describe the purification of the glycosylated TNF nor do they describe the pharmaceutical composition or the use of the same in treating human diseases. The examiner states that Allet describes the purification of TNF and concludes that it would be obvious to modify the methods disclosed by Korn to produce and purify the glycosylated TNF protein, obtain pharmaceutical compositions and use it in treating human disease in combination with the teachings of Allet. This rejection is respectfully traversed.

Korn has been discussed above. It does not produce biologically active TNF. The examples of Allet only produce recombinant TNF in *E. coli*. Furthermore, Allet states at column 26, lines 14-15:

> Mature human TNF is believed to be non-glycosylated.

Thus, neither Korn nor Allet suggest that the final product of any combination thereof would be glycosylated TNF. Thus, this is an unexpected result of the present invention which rebuts any *prima facie* case of obviousness. It should be noted that the present specification at page 5, lines 13-17, states that glycosylated TNF may have an increased half life in body

fluids and may improve binding to receptors and may be better protected against the influence of proteases. Thus, the unexpected existence of glycosylated TNF, which has never before been isolated and which has the proved properties over non-glycosylated TNF as described in the present specification, rebuts any *prima facie* case of obviousness and establishes the non-obviousness of the present invention. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Accordingly, it is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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Version with Markings to Show Changes Made

Claims 1, 2, 5 and 6 have been amended as follows:

1 (Amended). Isolated ~~biologically active~~ glycosylated human tumor necrosis factor having cytotoxic biological activity.

2 (~~Amended~~Twice-amended). A method for preparing isolated ~~biologically active~~ glycosylated human tumor necrosis factor exhibiting cytotoxic biological activity, comprising:

(a) ligating DNA encoding human TNF, or a ~~physiologically active variant~~ mutant thereof exhibiting cytotoxic biological activity, which mutant is capable of having its cytotoxic biological activity neutralized by antisera raised against human glycosylated TNF, to a replicable expression vehicle to obtain a replicable recombinant DNA comprising said DNA and said replicable expression vehicle;

(b) transforming eukaryotic cells with said replicable recombinant DNA to form transformants;

(c) culturing said transformants to cause said transformants to express said glycosylated human tumor necrosis factor; and

(d) isolating said glycosylated human tumor necrosis factor from the cultured transformants.

5 (~~Amended~~Twice-amended). A ~~pharmaceutical~~ composition consisting essentially of ~~an effective amount of biologically active~~ glycosylated human tumor necrosis factor having cytotoxic biological activity and at least one pharmaceutically acceptable carrier, diluent, or excipient.

6 (Amended). In the method for treating a human disease or condition treatable by the administration of an effective amount of human TNF alone or in combination with other active principles or inactive carriers, diluents or excipients, the improvement wherein said human TNF is ~~biologically active~~ glycosylated human TNF exhibiting cytotoxic biological activity.

Claims 7-12 have been added.

Page 1 of 2 [X] Original [ ] Supplemental Atty.Docket: MESSIKA=2

Combined Declaration f r Patent Applicati n and Power of Attorney

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and that I believe I am the original, first and sol inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PREPARATION OF GLYCOSYLATED TUMOR NECROSIS FACTOR

the specification of which (check one)

[ ] is attached hereto;

[ ] was filed in the United States under 35 U.S.C. §111 on _____, as USSN _____*; or

[XX] was/will be filed in the U.S. under 35 U.S.C. §371 by entry into the U.S. national stage of an international (PCT) application, PCT/IL98/00254; filed 01 June 1998, entry requested on _____*; national stage application received USSN _____*; §371/§102(e) date _____* (*if known), and was amended on _____ (if applicable).

(Include dates of amendments under PCT Art. 19 and 34 if PCT)

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above; and I acknowledge the duty to disclose to the Patent and Trademark Office (PTO) all information known by me to be material to patentability as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §§ 119, 365 of any prior foreign application(s) for patent or inventor's certificate, or prior PCT application(s) designating a country other than the U.S., listed below with the "Yes" box checked and have also identified below any such application having a filing date before that of the application on which priority is claimed:

(Number)	(Country)	(Day Month Year Filed)	[X] YES	[ ] NO
120979	Israel	02 June 1997		
			[ ] YES	[ ] NO

I hereby claim the benefit under 35 U.S.C. § 120 of any prior U.S. non-provisional Application(s) or prior PCT Application(s) designating the U.S. listed below, or under § 119(e) of any prior U.S. provisional applications listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in such U.S. or PCT application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the PTO all information as defined in 37 C.F.R. §1.56(a) which occurred between the filing date of the prior application and the national filing date of this application:

(Application Serial No.)	(Day Month Year Filed)	(Status: patented, pending, abandoned)
(Application Serial No.)	(Day Month Year Filed)	(Status: patented, pending, abandoned)

I hereby appoint the following attorneys, with full power of substitution, association, and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

SHERIDAN NEIMARK, REG. NO. 20,520 - ROGER L. BROWDY, REG. NO. 25,618 - ANNE M. KORNBAU, REG. NO. 25,884
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The undersigned hereby authorizes the U.S. Attorneys or Agents named herein to accept and follow instructions from INTERPHARM LABORATORIES LTD. as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. Attorney or Agent and the undersigned. In the event of a change of the persons from whom instructions may be taken, the U.S. Attorneys or Agents named herein will be so notified by the undersigned.

Atty.Docket: MESSIKA=2

Title: PREPARATION OF GLYCOSYLATED TUMOR NECROSIS FACTOR

U.S. Application filed _____, Serial No. _____

PCT Application filed 01 June 1998, Serial No. PCT/IL98/00254

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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POST OFFICE ADDRESS		
FULL NAME OF SIXTH JOINT INVNETOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		

ALL INVENTORS MUST REVIEW APPLICATION AND DECLARATION BEFORE SIGNING. ALL ALTERATIONS MUST BE INITIALED AND DATED BY ALL INVENTORS PRIOR TO EXECUTION. NO ALTERATIONS CAN BE MADE AFTER THE DECLARATION IS SIGNED. ALL PAGES OF DECLARATION MUST BE SEEN BY ALL INVENTORS.